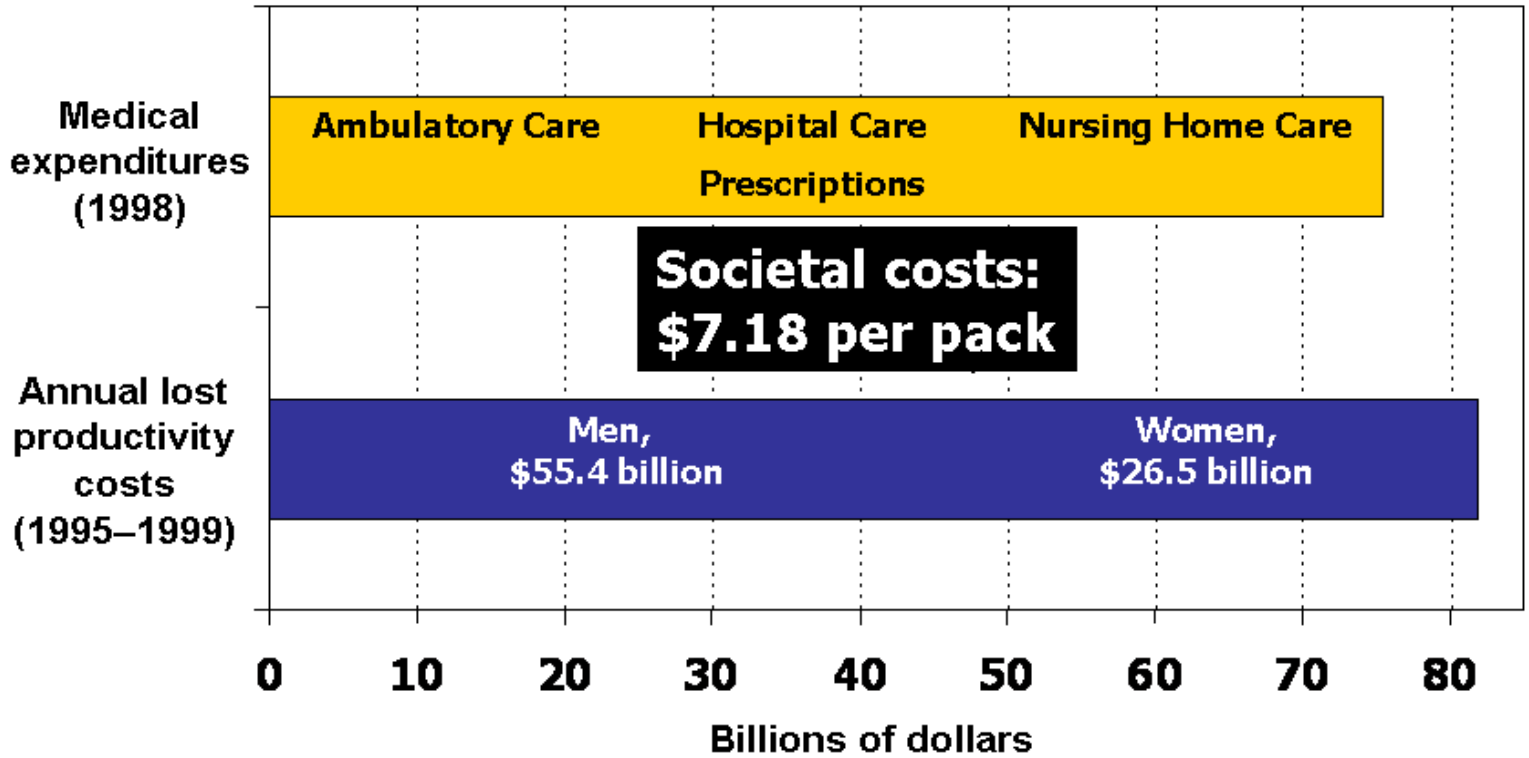
Pharmacotherapy of Tobacco Cessation Medication

Rx for Change: Clinician-Assisted Tobacco Cessation. San Francisco, CA: The Re
of
the University of California, University of Southern California, and Western
University of
Health Sciences, 1999-2008

Lecture Objectives

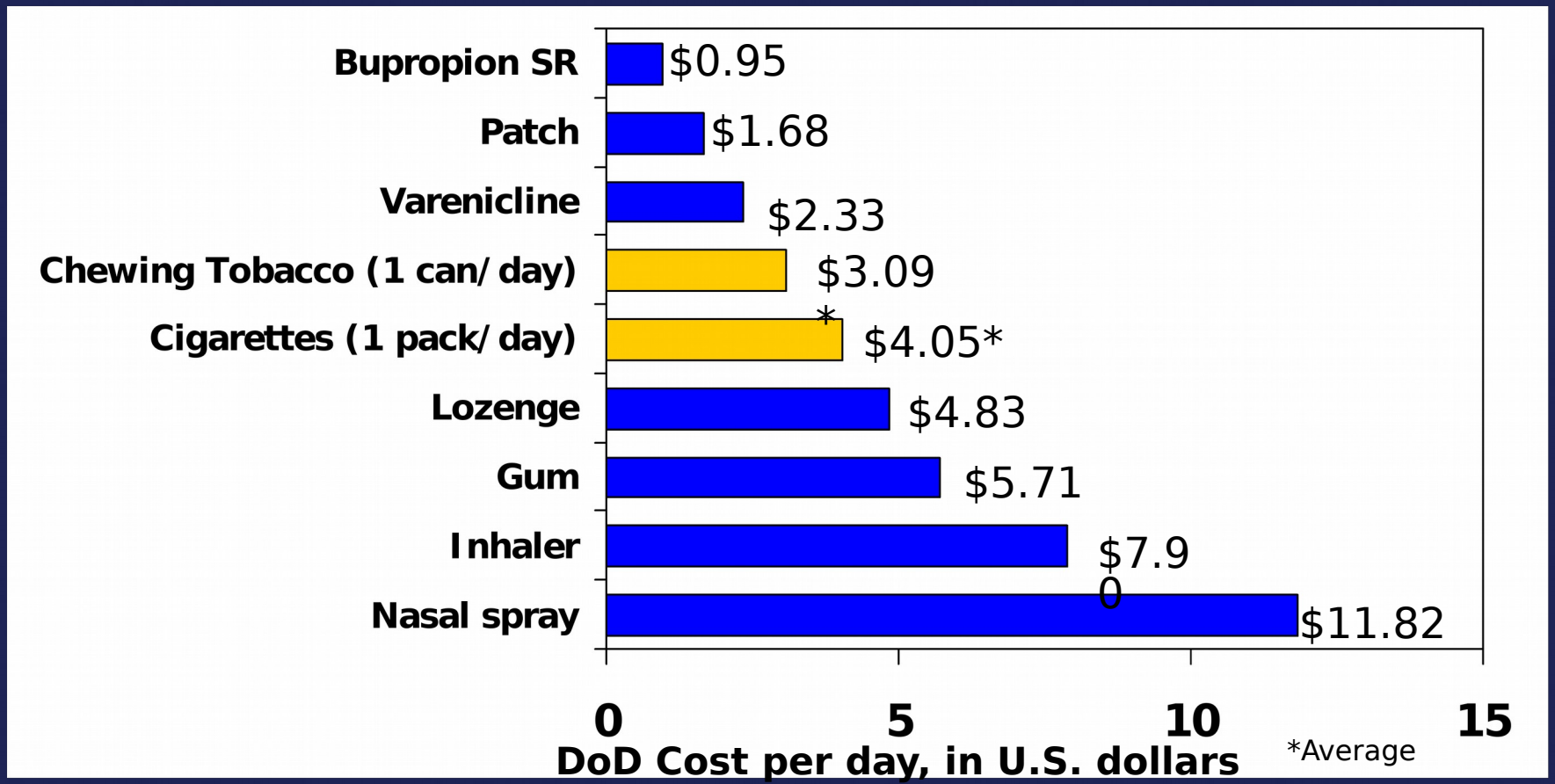
- Review the mechanism of action of Nicotine on the body
- Review first-line tobacco cessation pharmacotherapy medications
- Review the indications, contraindications, and major adverse affects of first-line tobacco cessation pharmacotherapies
- Instruct on the proper use of first line tobacco cessation medications
- Examine the efficacy and cost of available pharmocotherapies

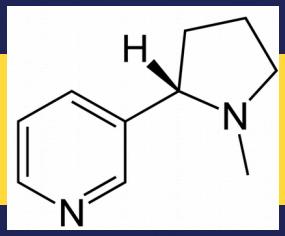
ANNUAL SMOKING-ATTRIBUTABLE ECONOMIC COSTS—U.S., 1995–1999



Centers for Disease Control and Prevention. (2002). *MMWR* 51:300–303.

COMPARATIVE DAILY COSTS of PHARMACOTHERAPY





Nicotine

Mechanism Of Action

- Absorbed via oral mucosa, lungs, GI mucosa, and skin
- Rapidly Distributes Throughout Body
- Cholinergic Receptor Agonist
- Dose Dependant Response
- Acts on CNS and Peripheral Nervous System
- Metabolized via the lung and liver

NICOTINE PHARMACODYNAMICS: WITHDRAWAL EFFECTS

- Depression
- Insomnia
- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite/weight gain
- Decreased heart rate
- Cravings*

Most symptoms peak 24–48 hr after quitting and subside within 2–4 weeks.

*Not considered a withdrawal symptom by *DSM*-IV criteria.

American Psychiatric Association. (1994). *DSM*-IV.
Hughes et al. (1991). *Arch Gen Psychiatry* 48:52–59.
Hughes & Hatsukami. (1998). *Tob Control* 7:92–93.

First Line Tobacco Cessation Medications

- **Three general classes of FDA approved drugs for smoking cessation:**
  - **Nicotine Replacement Therapy (NRT)**
    - Nicotine gum, patch, lozenge, nasal spray, inhaler
  - **Psychotropics**
    - Sustained-release bupropion
  - **Partial nicotine receptor agonist**
    - Varenicline

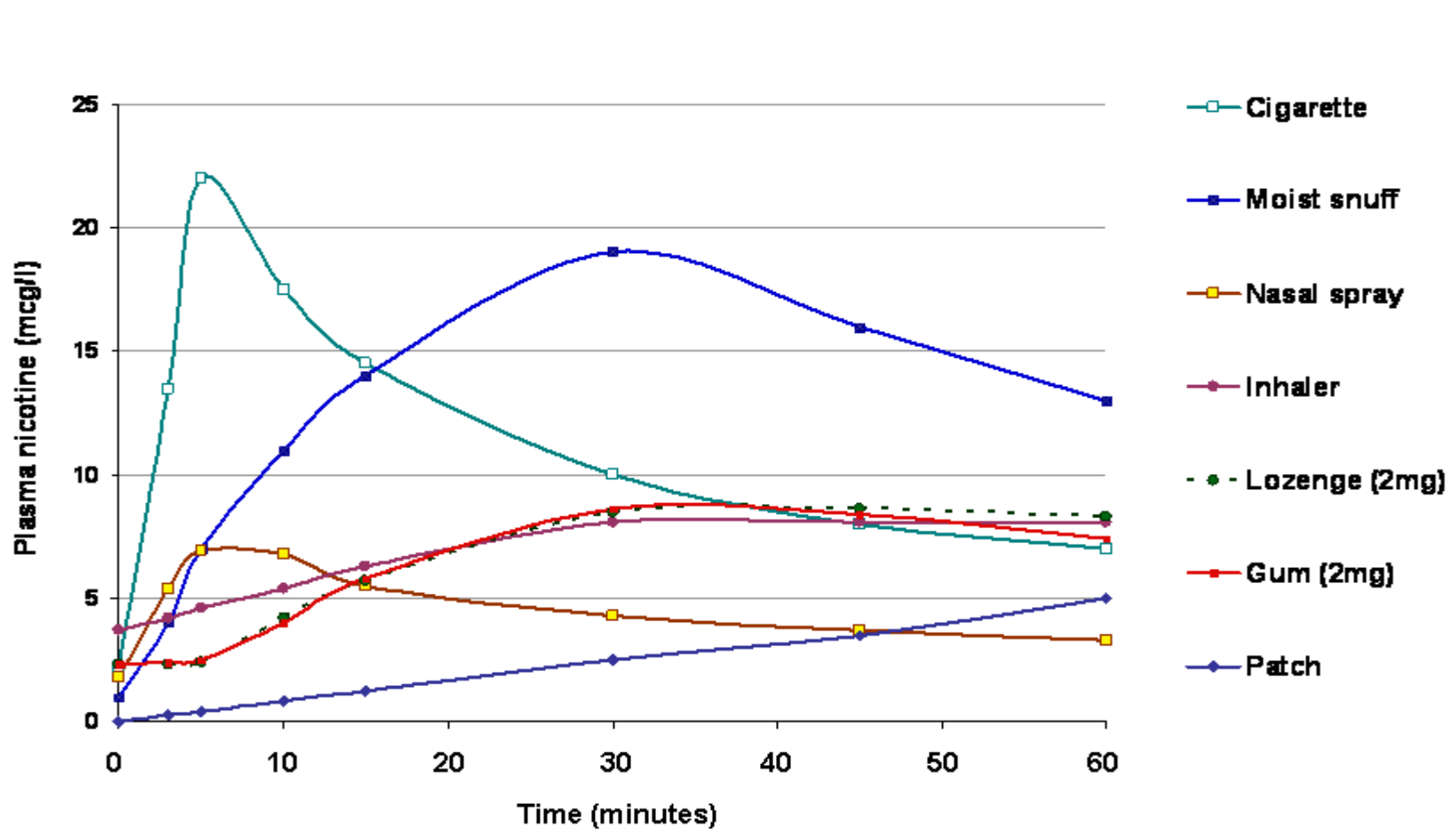
Currently, no medications have an FDA indication for use in spit tobacco cessation.

NRT: Rationale for Use

- Reduces physical withdrawal from nicotine
- Prevents exposure to carcinogens
- Less variable plasma nicotine concentrations

NRT APPROXIMATELY DOUBLES QUIT RATES.

Plasma Nicotine Concentrations for Various Nicotine-Delivery Systems



Source: Rx for Change: Clinician-Assisted Tobacco Cessation. San Francisco, CA: The Regent of the University of California, University of Southern California, and Western University of Health Sciences.;1999-2008

NRT Precautions

- Patients with underlying cardiovascular disease
  - Recent myocardial infarction (within past 2 weeks)
  - Serious arrhythmias
  - Serious or worsening angina

NRT products may be appropriate for these patients if they are under medical supervision.

NRT Precautions

atients with other underlying conditions

- Pregnancy
- Lactation
- Active temperomandibular joint disease (gum o

NRT products may be appropriate for these patients if they are under medical supervision.

NRT: Other Considerations

- **NRT is not FDA-approved for use in children or adolescents**
- **Nonprescription sales (patch, gum, lozenge) are restricted to adults ≥18 years of age**
  - NRT use in minors requires a prescription
- **Patients should stop using all forms of tobacco upon initiation of the NRT regimen**

NRT Options

Patch (OTC)

Gum (OTC)

Lozenge (OTC)

Nasal Spray (Rx)

Oral Inhaler (Rx)

TRANSDERMAL NICOTINE PATCH

- Nicotine is well absorbed across the skin
- Delivery to systemic circulation avoids hepatic first-pass metabolism
- Plasma nicotine levels are lower and fluctuate less than with smoking

TRANSDERMAL NICOTINE PATCH: DOSING AND ADMINISTRATION

DOSING

- **Smoking history over 10 cigarettes per day:**
  Usual dose follows a 10 week schedule:
  Weeks 1-6, use one 21 milligram patch per day
  Weeks 7-8, use one 14 milligram patch per day
  Weeks 9-10, use one 7 milligram patch per day

- **Smoking history 10 or fewer cigarettes per day :**
  Usual dose follows an 8 week schedule:
  Weeks 1-6, use one 14 milligram patch per day
  Weeks 7-8, use one 7 milligram patch per day

ADMINISTRATION

- **Apply one new patch at the same time every day.**
- **Apply to a site that is dry, clean, and hairless.**
- **Wash hands after applying or removing patch.**
- **Wear the patch for 16 or 24 hours.**
- **If you crave cigarettes when you wake up, wear the patch for 24 hours.**
- **If you have vivid dreams or other sleep disturbances, remove the patch at bedtime and apply a new one in the morning.**

TRANSDERMAL NICOTINE PATCH: SUMMARY

ADVANTAGES

- Steady-state nicotine levels are achieved throughout the day.
- The patch is easy to use and conceal.
- Fewer compliance issues are associated with the patch.

DISADVANTAGES

- Patients cannot titrate the dose.
- Allergic reactions to the adhesive may occur.
- Patients with dermatologic conditions should not use the patch.

NICOTINE GUM

- **Resin complex**
  - Nicotine
  - Polacrilex
- **Sugar-free chewing gum base**
- **Contains buffering agents to enhance buccal absorption of nicotine**
- **Available: 2 mg, 4 mg; regular and flavored varieties**
- **Can flavor with crushed menthol cough drops**

NICOTINE GUM:
DOSING AND ADMINISTRATION

DOSING

Initial dose, smoking history

under 25 cigarettes a day: Use 2mg
over 25 cigarettes a day: Use 4mg

Usual dose, following a 12 week schedule:

Week 1 to 6: 1 piece every 1 to 2 hours
Week 7 to 9: 1 piece every 2 to 4 hours
Week 10 to 12: 1 piece every 4 to 8 hours

Maximum dose, 24 pieces a day

ADMINISTRATION

- **Squeeze- Do not chew like you would regular gum.**
- **Squeeze the gum three times then park in the oral mucosa**
- **Move the piece of gum to the side of your mouth, between your gum and your cheek.**
- **Leave the gum there until the tingling goes away.**
- **Slowly start to chew the gum again until the tingling returns. Then move the gum to the side of your mouth again.**
- **Keep repeating this cycle of slowly chewing, then moving the gum to the side of your mouth.**

NICOTINE GUM: Summary

ADVANTAGES

- Gum may satisfy oral cravings.
- Gum may delay weight gain.
- Patients can titrate therapy to manage withdrawal symptoms

DISADVANTAGES

- Gum chewing may not be socially acceptable
- Gum my be difficult to use with dentures
- Patients must utilize proper technique to minimize adverse effects

NICOTINE LOZENGE

- Nicotine polacrilex formulation
- Delivers ~25% more nicotine than equivalent gum dose
- Sugar-free, mint or cherry flavor (boxed or POP-PAC)
- Contains buffering agents to enhance buccal absorption of nicotine
- Available: 2 mg, 4 mg

NICOTINE LOZENGE: DOSING AND ADMINISTRATION

DOSING

- 4-mg strength: for individuals who smoke their first cigarette within 30 minutes of waking up.
- 2-mg strength: for those who smoke their first cigarette after 30 minutes of waking.
- Week 1 - 6: One lozenge every 1 to 2 hours.
- Week 7 - 9: One lozenge every 2 to 4 hours during.
- Week 10 – 12: One lozenge every 4 to 8 hours.

ADMINISTRATION

- The lozenge should be sucked on until it dissolves; it should not be bitten or chewed or swallowed
- Eating or drinking should be avoided for 15 minutes prior to use of the lozenges.

NICOTINE LOZENGE: SUMMARY

ADVANTAGES

- Lozenge use may satisfy oral cravings.
- The lozenge is easy to use and conceal.
- Patients can titrate therapy to manage withdrawal symptoms.

DISADVANTAGES

- Gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome.

NICOTINE NASAL SPRAY

- Aqueous solution of nicotine in a 10-ml spray bottle
- 50 µL spray / 0.5mg nicotine per metered dose
- ~100 doses/bottle
- Rapid absorption across nasal mucosa

NICOTINE NASAL SPRAY
DOSING AND ADMINISTRATION

DOSAGE SUMMARY

- One dose is equal to 2 sprays (1 per nostril) (0.5 mg/spray or 1 mg/dose)
- Usual dose follows a 14 week schedule
- Weeks 1-8, start with 1 or 2 doses per hour for 6 to 8 weeks, but at least 8 doses per day
- Weeks 9-14, gradually reduce over 4 to 6 weeks; no optimal tapering schedule described
- Maximum dose, 5 doses per hour or 40 doses per day

ADMINISTRATION

- Do not to sniff, swallow, or inhale through the nose as the spray is being administered.
- Administer the spray with the head tilted back slightly.
- The dose should be gradually tapered by decreasing to one spray/dose (0.5 milligrams of nicotine) or increasing the interval between doses though no optimal tapering schedule is described.
- The maximum recommended duration of treatment is 6 months

NICOTINE NASAL SPRAY: SUMMARY

ADVANTAGES

- Patients can easily titrate therapy to rapidly manage withdrawal symptoms.

DISADVANTAGES

- Nasal/throat irritation may be bothersome.
- Nasal spray has higher dependence potential.
- Patients with chronic nasal disorders or severe reactive airway disease should not use the spray.

NICOTINE INHALER

- **Nicotine inhalation system consists of:**

  - Mouthpiece
  - Cartridge with porous plug containing 10 mg nicotine

- **Delivers 4 mg nicotine vapor, absorbed across buccal mucosa**
- **May satisfy hand-to-mouth ritual of smoking**
- **Recommended for smokers who have a high behavioral dependence and smoke 20 or fewer cigarettes per day**

NICOTINE INHALER: DOSING AND ADMINISTRATION

DOSAGE SUMMARY

- One 10-mg cartridge delivers 4 mg nicotine
- Usual dose, involves 3-6 month protocol:

  - Weeks 1 through 12, use 6 to 16 cartridges daily

  - Weeks 13 through 24, gradually reduce over next 6 to 12; no optimal taper

- Maximum dose, 16 cartridges daily.

ADMINISTRATION

- Nicotine vapor inhaled through the mouthpiece is absorbed buccally rather than through the lungs.
- Each cartridge provide about 20 minutes of active puffing, or approximately 80 deep draws or about 300 shallow puffs.
- A therapeutic effect is best achieved by frequent continuous puffing (20 minutes).
- Ten puffs on the inhaler provides approximately the same amount of nicotine contained in one puff of a cigarette

NICOTINE INHALER: SUMMARY

ADVANTAGES

- Patients can easily titrate therapy to manage withdrawal symptoms.
- The inhaler mimics the hand-to-mouth ritual of smoking.

DISADVANTAGES

- The initial throat or mouth irritation can be bothersome.
- Cartridges should not be stored in very warm conditions or used in very cold conditions.
- Patients with underlying bronchospastic disease must use the inhaler with caution.

BUPROPION SR

- Wellbutrin 150mg SR
- Can use 100mg
- Non-nicotine cessation aid
- Sustained-release antidepressant
- Oral formulation

BUPROPION: MECHANISM of ACTION

- **Atypical antidepressant thought to affect levels of various brain neurotransmitters**

  - Dopamine
  - Norepinephrine

- **Clinical effects**

  - ↓ craving for cigarettes
  - ↓ symptoms of nicotine withdrawal

BUPROPION: CONTRAINDICATIONS

- Patients with a seizure disorder
- Patients taking
  - Wellbutrin, Wellbutrin SR, Wellbutrin XL
  - MAO inhibitors in preceding 14 days
- Patients with a current or prior diagnosis of anorexia or bulimia nervosa
- Patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)

BUPROPION: WARNINGS and PRECAUTIONS

Bupropion should be used with extreme caution in the following populations:

- Patients with a history of seizure
- Patients with a history of cranial trauma
- Patients taking medications that lower the seizure threshold
  antipsychotics, antidepressants, theophylline, systemic steroids)
- Patients with severe hepatic cirrhosis

BUPROPION: USE in PREGNANCY

- Category C drug
- Use only if clearly indicated
- Attempt nondrug treatment first

BUPROPION SR: DOSING

Patients should begin therapy 1 to 2 weeks PRIOR to their quit date to ensure that therapeutic plasma levels of the drug are achieved.

Initial treatment

- 150 mg po q AM x 3 days

Then…

- 150 mg po bid
- Duration, 7–12 weeks

BUPROPION: ADVERSE EFFECTS

- Common side effects include the following:
  - -Insomnia (avoid bedtime dosing)
  - -Dry mouth

- Less common but reported effects:
  - -Tremor
  - -Skin rash

BUPROPION SR: SUMMARY

ADVANTAGES

- Bupropion is an oral formulation with twice-a-day dosing.
- Bupropion might be beneficial for patients with depression.

DISADVANTAGES

- The seizure risk is increased.
- Several contraindications and precautions preclude use.

VARENICLINE

- Non-nicotine cessation aid
- Partial nicotinic receptor agonist
- Oral formulation

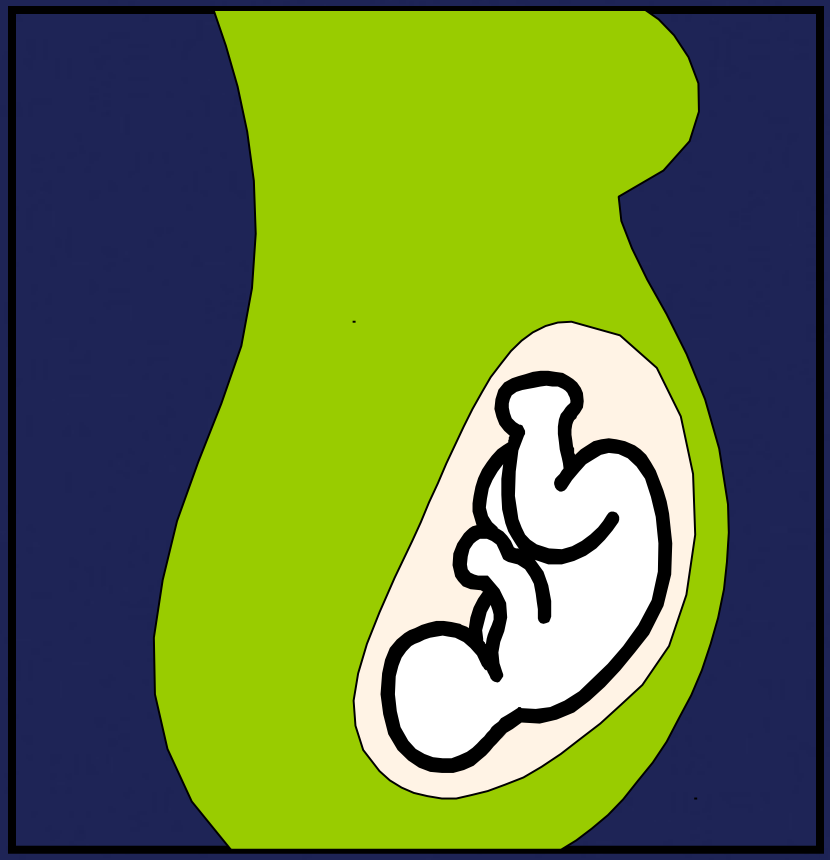
VARENICLINE: MECHANISM of ACTION

- Binds with high affinity and selectivity at $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors
  - Stimulates low-level agonist activity
  - Competitively inhibits binding of nicotine

- Clinical effects
  - ↓ symptoms of nicotine withdrawal
  - Blocks dopaminergic stimulation responsible for reinforcement & reward associated with smoking

VARENICLINE : USE in PREGNANCY and LACTATION

- Category C drug
- Use only if potential benefit justifies potential risk
- Attempt nondrug treatment first
- Unknown if drug excreted in human breast milk



VARENICLINE: DOSING

Patients should begin therapy 1 week PRIOR to their quit date. The dose is gradually increased to minimize treatment-related nausea and

	Treatment Day	Dose
Initial dose titration	Day 1 to day 3	0.5 mg qd
	Day 4 to day 7	0.5 mg bid
	Day 8 to end of treatment*	1 mg bid

* Up to 12 weeks

VARENICLINE: ADVERSE EFFECTS

Common side effects (≥5% and twice the rate observed in placebo-treated patients) include:

- Nausea
- Sleep disturbances (insomnia, abnormal dreams)
- Constipation
- Flatulence
- Vomiting

VARENICLINE: ADDITIONAL PATIENT EDUCATION

- Doses should be taken after eating, with a full glass of water

- Nausea and insomnia are side effects that are usually temporary.

  - If symptoms persist, notify your health care provider

- Dose tapering not necessary when discontinuing treatment

VARENICLINE: SUMMARY

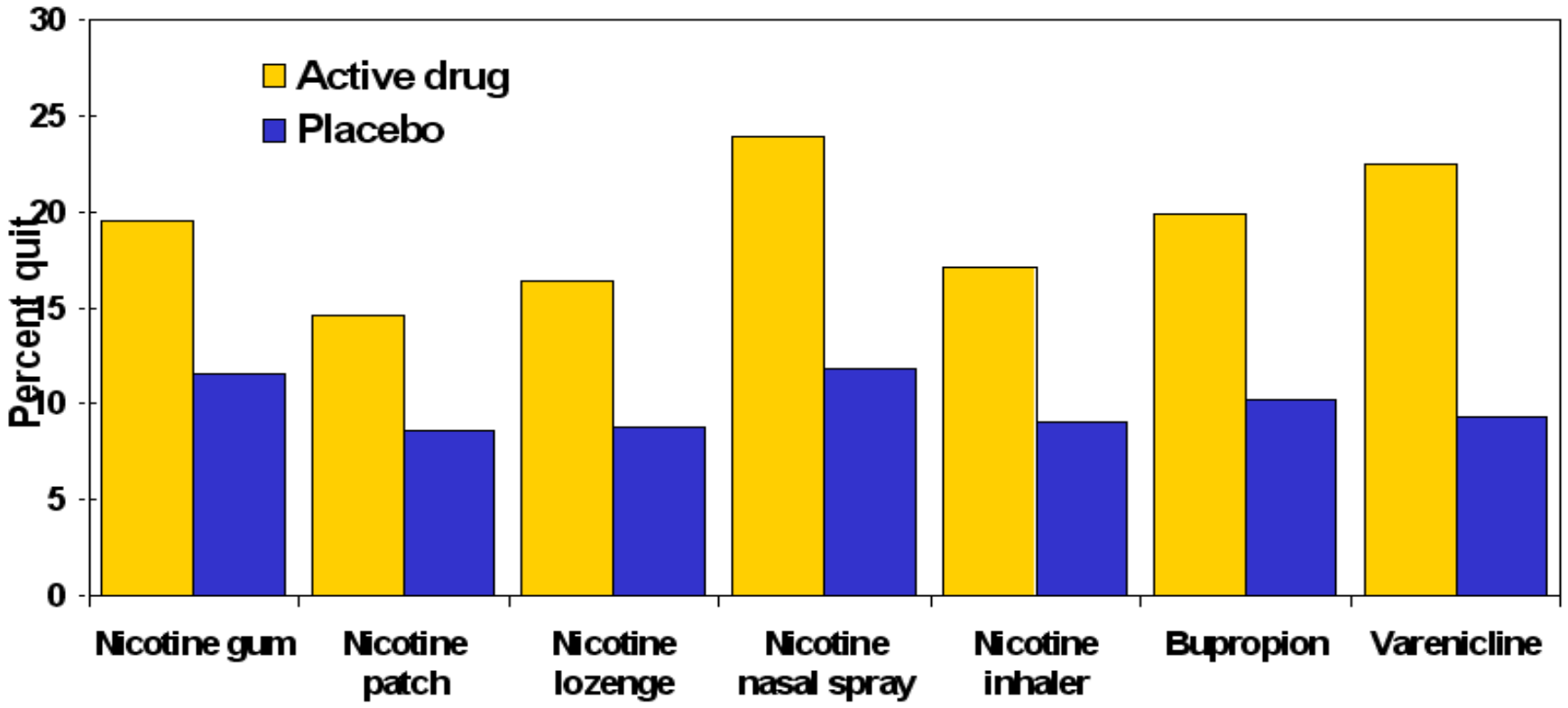
ADVANTAGES

- Varenicline is an oral formulation with twice-a-day dosing.
- Varenicline offers a new mechanism of action for persons who previously failed using other medications.

DISADVANTAGES

- May induce nausea in up to one third of patients.
- Post-marketing surveillance data not yet available.

LONG-TERM (≥6 month) QUIT RATES for AVAILABLE CESSATION MEDICATIONS



Data adapted from Silagy et al. (2004). *Cochrane Database Syst Rev;* Hughes et al., (2004). *Cochrane Database Syst Rev.;* Gonzales et al., (2006). *JAMA* and Jorenby et al., (2006). *JAMA*

COMBINATION PHARMACOTHERAPY

- **Combination NRT**

  -Long-acting formulation (patch)

  -Produces relatively constant levels of nicotine

  PLUS

  -Short-acting formulation (gum, lozenge, inhaler, nasal spray)

  -Allows for acute dose titration as needed for withdrawal symptoms

- **Bupropion SR + NRT**
- **The safety and efficacy of combination of varenicline with NRT or bupropion has not been established.**

COMPLIANCE IS KEY to QUITTING

- Promote compliance with prescribed regimens.
- Use according to dosing schedule, NOT as needed.
- Inform the patient:

"When you use a cessation product it is important to read all the directions thoroughly before using the product. The products work best in alleviating withdrawal symptoms when used correctly, and according to the recommended dosing schedule."

The RESPONSIBILITY of HEALTH PROFESSIONALS

It is **inconsistent**

to provide health care and

—at the same time—

remain silent (or inactive)

about a major health risk.